High prevalence of polycystic ovary syndrome characteristics in girls with euthyroid chronic lymphocytic thyroiditis: a case–control study

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Abstract

Objective: The aim was to find the prevalence of polycystic ovary syndrome (PCOS) phenotype in adolescent euthyroid girls with chronic lymphocytic thyroiditis (CLT).

Design: This was a prospective case–control study as part of an ongoing community-wide thyroid survey in Indian schools.

Methods: One hundred and seventy-five girls with euthyroid CLT and 46 age-matched non-CLT girls underwent clinical, biochemical, hormonal, and ultrasonographic evaluation for diagnosis of PCOS by Rotterdam 2003 criteria. All subjects underwent serum sampling for LH, FSH, testosterone, DHEAS, free thyroxine, TSH, and anti-thyroid peroxidase (TPO) antibodies. Oral glucose tolerance test (OGTT) was undertaken for plasma glucose and insulin.

Results: Significantly higher prevalence of PCOS was noted in girls with euthyroid CLT when compared to their control counterparts (46.8 vs 4.3%, \( P < 0.001 \)). The CLT girls had higher body mass index, waist circumference, and systolic blood pressure \(( P < 0.001 \)) . Mean number of menstrual cycles/year was 8.4±3.5 vs 10.1±1.4, and mean Ferriman–Gallwey score was 11.9±3.5 vs 3.0±2.4 \(( P < 0.001 \)) in cases versus controls respectively. The fasting and postprandial glucose and serum cholesterol were also higher in the cases \(( P < 0.001 \)) . Homeostasis model assessment-insulin resistance was 4.4±4.2 vs 2.3±2.7 in the cases versus controls \(( P < 0.001 \)) .

Conclusion: Higher prevalence of PCOS characteristics in euthyroid CLT girls when compared to controls suggest possible role of autoimmune phenomenon in the etiopathogenesis of PCOS. Further studies are required to understand the pathogenic link between these two disorders.

Introduction

Polycystic ovary syndrome (PCOS) is one of the most common endocrine disorders in women of reproductive age, affecting about 6.5–6.7% of all premenopausal women (1, 2). The disorder originally described as cystic disease of the ovaries by Stein & Levanthal (3) is now considered to be associated with a barrage of endocrine and metabolic disturbances such as hypertension, impaired glucose tolerance (IGT), type 2 diabetes mellitus, coronary artery disease, increased risk of endometrial and perhaps breast cancer (4). The main endocrine derangements responsible for the clinical manifestations are hyperandrogenemia and abnormal insulin response to glucose (5, 6). Insulin resistance (IR)/hyperinsulinemia in PCOS being the main pathogenic defect is also supported by clinical, biochemical, and hormonal response to insulin sensitizers (7, 8). With adipose tissue being one of the important sources of pro-inflammatory cytokines, IR in obese has been attributed to elevation of adipocytokines and other inflammatory markers. Women with PCOS have been demonstrated to have elevated cytokines like tumour necrosis factor-\( \alpha \) (TNF-\( \alpha \)) and IL-6 concentrations independent of obesity, and these alterations in serum inflammatory markers in PCOS are unrelated to PPAR-\( \gamma \) variants (9). It has been demonstrated that the therapy with metformin in PCOS leads to an increase in plasma adiponectin and TNF-\( \alpha \) but not plasma IL-6 and C reactive protein (CRP) (10). Some authors demonstrated a high prevalence of autoimmune thyroiditis in PCOS women suggesting a potential pathogenic link with autoimmunity/sub-inflammatory thyroiditis (11). Thus, the concept that inflammatory and immune markers may have a role in the pathogenesis of IR and hyperinsulinemia in PCOS has taken a front seat.

Chronic lymphocytic thyroiditis (CLT) is the most prevalent cause of hypothyroidism in areas with sufficient iodine intake, and is characterized by high levels of thyroid autoantibodies, lymphocytic infiltration.
of the thyroid gland, and a typical hypoechoic pattern on thyroid ultrasound. High prevalence of CLT in
Down’s, and Turner’s syndromes (12), and its associ-
ation with the HLA DR3, DR5, and HLA DRB1*1404
genes (13, 14) suggests that CLT may have a genetic
contribution. Similarly, the evidence of a strong familial
association in the first-degree relatives of PCOS subjects
suggests a role of genetics in its etiopathogenesis, and
several genes have been identified to date (15–17).
Since both these disorders have a similar pathogenic
mechanism comprising of familial aggregation, subin-
flammation/inflammation, and elevated adipocytok-
ines, we speculate that there may be a potential
cross-link between the two conditions.

Since no systematic analysis of PCOS phenotype in
women with CLT has been undertaken to date, we
therefore planned this prospective case–control study
to understand the association between these two
genetically predisposed inflammatory disorders.

Subjects and methods

Study participants
The study was conducted in 13–18-year-old girls
identified during a country-wide survey of thyroid
diseases in schools and in those who reported to the
outpatient department of our institutes. Informed
consent was taken from the parents of all the children
studied. The study protocol was approved by the ethics
committee of the Institute of Nuclear Medicine and
Allied Sciences, New Delhi.

Two hundred consecutive girls with fine-needle
aspiration cytology (FNAC) and antibody-proven CLT
(cases) were enrolled for the study. These girls were then
evaluated for any evidence of PCOS on the basis of
Rotterdam 2003 criteria as follows: i) clinical and/or
biochemical hyperandrogenism, ii) oligo-anovulation,
and iii) polycystic ovaries on ultrasonography (18),
after excluding girls with suggestion of nonclassical
congenital adrenal hyperplasia. Cushing’s syndrome,
hyperprolactinemia, androgen-secreting tumors or
androgen intake. Forty-six age-matched apparently
healthy euthyroid non-CLT girls from the same school
survey group were taken as controls. These girls had
normal cytology or colloid goiter on FNAC, negative
anti-TPO antibody, and normal thyroid echogenicity on
ultrasonography (USG). Subjects suffering from any
systemic illness and those with a history of receiving
any drugs known to interfere with thyroid function,
hypothalamo-pituitary axis, insulin sensitivity, or
glucose tolerance were excluded from the study.

Methods
The study girls were subjected to detailed history,
clinical examination, biochemical, hormonal, cyto-
pathological, and sonographic evaluation. FNAC was
performed under aseptic conditions by using a 23-G
needle, and USG thyroid was done by a single operator
who was blinded to the clinical and biochemical status
of the subjects. The echogenicity of the thyroid gland
was assessed in relation to the surrounding neck
muscles, and the brightness gain was adjusted for
optimum visualization of the thyroid parenchyma. USG
abdomen was done by the same observer to study
polycystic ovarian morphology and to rule out any
adrenal or ovarian mass lesion. The diagnosis of
PCOS on transabdominal USG was based on the
presence of >12 peripheral follicles each 2–9 mm in
diameter in one or both ovaries, increased ovarian
volume (>10 cm) on one or both sides and thecal
hyperechogenicity in the mid-follicular phase.

For making a positive diagnosis of PCOS, all these
subjects were interviewed to furnish details of men-
strual history including age of menarche, regularity,
and duration of cycles, number of cycles per year
or intermenstrual interval. Oligomenorrhea was
defined as intermenstrual interval of ≥35 days or a
total of ≤8 menses per year. Amenorrhea was defined
as the absence of menstruation for the last 6 or more
months. Quantification of hirsutism was done using
modified Ferriman–Gallwey (F–G) score by counting
of nine body areas by a single observer with good
reproducibility (19). A score of ≥8 of 36 was taken
as significant.

Investigation
Both case and control subjects underwent oral glucose
tolerance test between 0800 and 0900 h with 75-g
glucose load after an overnight (10–12 h) fast and a
normal diet for at least 3 days prior to testing. The
fasting sample was taken in the follicular phase of
spontaneous or medroxyprogesterone-induced cycle for
baseline biochemistry, anti-TPO antibodies, glucose,
lipids, insulin, hormones, and thyroid profile. Samples
for plasma glucose and insulin were also collected 2 h
after the glucose load. Plasma glucose was assayed
by enzymatic calorimetric method (GOD-POD, Roche).
Hemogram, renal, and liver function tests were done
for both controls and CLT subjects. Hormonal
evaluation included LH, FSH, prolactin, testosterone,
DHEAS, serum cortisol (0800/1600 h or after
overnight dexamethasone suppression test, in cases
of diurnal rhythm was reversed or serum cortisol levels
were raised), and 17-hydroxyprogesterone (17-OHP)
estimations. Serum 17-OHP levels <4.8 ng/ml were
taken as normal, and ACTH stimulation was done if the
levels were from 4.8 to 10 ng/ml. Free thyroxine (FT4).
TSH, anti-TPO antibody, and insulin were estimated
by electrochemiluminescence assay (Elecsys Roche
Diagnostics) and LH, FSH by IRMA (Radium, Italy).
Serum cortisol, serum testosterone, DHEAS, 17-OHP,
and prolactin were assayed by RIA (Radium, Italy).
The analytical sensitivity, intra-assay and inter-assay
coefficients of variation were within the manufacturer’s prescribed limits. Transabdominal ultrasound was performed using a 3.5 MHz transducer (HD1-5000 Phillips, Bothel, WA, USA) and thyroid USG using portable equipment with 7.5 MHz transducer (Aloka SSD-500, Tokyo, Japan). Thyroid gland was considered hypoechogenic when its signal was equal or below that of the surrounding neck muscles.

Calculations

Glucose intolerance was graded according to the ADA guidelines, and homeostasis model assessment-IR (HOMA-IR) was calculated as follows: fasting insulin (mU/l) × fasting glucose (mmol/l)/22.5 (20). Anti-TPO antibodies were considered positive when the levels were above 34 U/ml. Biochemical hyperandrogenism was defined as a serum testosterone >0.65 ng/ml.

Statistical analysis

The statistical analysis was performed with SPSS version 11.5 (Chicago, IL, USA). The quantitative variables have been described as mean ± s.d. To compare quantitative variables between two groups, unpaired t-test was used. The χ² test/Fischer’s exact test was used to compare the qualitative variables. Comparison between controls, PCOS, and non-PCOS subgroups of CLT girls was done by ANOVA. FT4 quartiles were correlated with the presence of PCOS components using Pearson’s correlation. P<0.05 was considered significant.

Results

Of the 200 euthyroid CLT girls recruited for the study, only 175 girls, whose data were complete, were analyzed. The clinical, biochemical, and hormonal parameters of the study and control subjects are presented in Tables 1 and 2. Diagnosis of PCOS by Rotterdam 2003 criteria was established in 82/175 girls (46.85%) with proven CLT and 2/46 (4.32%) in controls. Since the diagnosis of PCOS in adolescent girls is considered to be relatively difficult (21), we therefore adopted more stringent criteria recommended by Sultan & Paris (22) and found a similar prevalence of PCOS (45.9%) in girls with CLT. Mean anti-TPO antibody levels as expected were significantly higher in subjects than in controls (321.4 ± 189.6 vs 22.5 ± 7.2, P=0.001). The average number of menstrual cycles/year was significantly lower in cases as compared to controls (8.4 ± 3.5 vs 10.1 ± 1.4, P=0.001). Among the CLT group, ten patients had spells of amenorrhea, and four others had more than eight cycles/year but their cycles were grossly irregular. Mean F–G score was 11.9 ± 3.5 vs 3.0 ± 2.4 (P=0.001). F–G score of more than eight was present in 111/175 (63.42%) of cases as compared to 3/46 (6.52%) controls. Acne vulgaris affected 24/175 (13.71%) cases with grade I in 9.7% and grade II in 4% of cases. Hypertension, defined as BP ≥ 135/85 mmHg, was present in 22/175 (12.57%) of cases and none of the controls. The girls with CLT had significantly higher systolic blood pressures, higher body mass index (BMI), and wider waist circumference (P=0.001, 0.001, and 0.02 respectively). The fasting and postprandial plasma glucose and serum cholesterol were also higher in the CLT girls than in controls (P=0.001, 0.001, and 0.001 respectively). Fourteen cases (8%) had impaired fasting plasma glucose, 13 (7.4%) had IGT, and only one patient had diabetes mellitus. The serum LH/FSH ratio, serum testosterone, and fasting insulin were also significantly higher in the cases than in the controls (P=0.003, 0.001, and 0.005 respectively). More than 18.85% (33/175) cases and 4.34% (2/46) controls had an elevated (≥ 2) LH/FSH ratio. Serum total testosterone >0.65 ng/ml was observed in 48.57% (85/175) cases and 10.86% (5/46) controls. However, when the serum testosterone cut-off was taken as 0.7 ng/ml, the respective observations were 45.7% in cases and 9.98%...
in controls, which were statistically insignificant (P = 0.29 among cases and 0.50 among controls).

IR as calculated by HOMA-IR was 4.4 ± 2.2 and 2.3 ± 2.7 in cases and controls respectively (P = 0.001), and consequently, HOMA-IR > 2 was observed in a significantly higher percentage of cases than of controls (91/175 (52%) vs 9/46 (19.56%) (P = 0.001)). Though fasting serum insulin ≥14 µIU/ml was present in 94/175 (53.71%) cases when the fasting insulin cutoff was brought down to 10 µIU/ml, a significantly higher number of subjects (146/175 (83.42%)) qualified for the presence of IR. Number of menstrual cycles, hirsutism score, serum testosterone, fasting and post-prandial glucose correlated positively with fasting serum insulin and HOMA-IR. Even after adjusting for BMI, the number of menstrual cycles per year (8.6 ± 3.4 vs 9.9 ± 1.5; P = 0.03), F-G score (10.71 ± 2.8 vs 3.0 ± 2.4; P = 0.001), serum total testosterone (0.7 ± 0.38 vs 0.48 ± 0.18 ng/ml; P = 0.002), fasting serum insulin (21.01 ± 18.3 vs 13.02 ± 13.8 µIU/ml; P = 0.02) and HOMA-IR values (14.12 ± 3.89 vs 2.26 ± 2.51; P = 0.009) were significantly different in cases when compared to controls.

On categorization of CLT girls based on Rotterdam 2003 criteria, two distinct subgroups (PCOS versus non-PCOS) emerged whose clinical, biochemical, and endocrine parameters differed both within themselves and from the control group (Table 3). On correlating the serum FT₄ levels with various components of PCOS, FT₄ quartiles showed a significant inverse correlation with PCOS components (r = −0.46, P = 0.05). Thirteen PCOS girls (7.4%) had their serum FT₄ in the highest quartile, whereas 27 (15.42%) non-PCOS girls had the serum FT₄ in this quartile (Fig. 1).

Table 2 Comparison of biochemical and hormonal characteristics of cases versus control girls.

<table>
<thead>
<tr>
<th>Characteristics (normal range)</th>
<th>Cases n = 175</th>
<th>Controls n = 46</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>BGF (&lt;100 mg/dl)</td>
<td>81.4 ± 13.7 (53–127)</td>
<td>69.1 ± 5.9 (56–84)</td>
<td>0.01</td>
</tr>
<tr>
<td>BGGP (&lt;140 mg/dl)</td>
<td>107.1 ± 19.4 (78–187)</td>
<td>91.5 ± 7.1 (76–105)</td>
<td>0.001</td>
</tr>
<tr>
<td>Cholesterol (150–200 mg/dl)</td>
<td>197.4 ± 30.1 (78–283)</td>
<td>148.8 ± 24.8 (89–198)</td>
<td>0.001</td>
</tr>
<tr>
<td>Free T₄ (nmol/dl)</td>
<td>15.7 ± 2.8 (10.2–25.5)</td>
<td>15.9 ± 3.0 (11.9–22.8)</td>
<td>0.44</td>
</tr>
<tr>
<td>TSH (0.5–5.5 IU/ml)</td>
<td>2.4 ± 1.4 (0.03–7.0)</td>
<td>3.0 ± 1.0 (1.3–5.3)</td>
<td>0.06</td>
</tr>
<tr>
<td>Anti-TPO (0–35 IU/l)</td>
<td>321.4 ± 189.6 (5–600)</td>
<td>22.5 ± 7.2 (8–33)</td>
<td>0.001</td>
</tr>
<tr>
<td>LH (7–22 IU/l)</td>
<td>11.5 ± 4.6 (25.3–34.4)</td>
<td>8.2 ± 3.0 (4.11–21.3)</td>
<td>0.001</td>
</tr>
<tr>
<td>FSH (7–22 IU/l)</td>
<td>6.2 ± 2.9 (1.9–17.2)</td>
<td>7.2 ± 4.3 (2.01–21.36)</td>
<td>0.128</td>
</tr>
<tr>
<td>LH/FSH (&lt;2)</td>
<td>2.4 ± 1.6 (0.18–10.2)</td>
<td>1.6 ± 1.2 (0.12–5.17)</td>
<td>0.003</td>
</tr>
<tr>
<td>Testosterone (0.12–70 ng/ml)</td>
<td>0.8 ± 0.5 (0.23–1.99)</td>
<td>0.5 ± 0.2 (0.21–0.82)</td>
<td>0.001</td>
</tr>
<tr>
<td>DHEAS (1.2–3.6 ng/ml)</td>
<td>4.2 ± 4.7 (0.91–22)</td>
<td>1.6 ± 0.5 (0.4–3.55)</td>
<td>0.001</td>
</tr>
<tr>
<td>Cortisol (µg/dl) (morning)</td>
<td>14.1 ± 3.9 (4.17–27.7)</td>
<td>8.1 ± 5.6 (0.51–18.5)</td>
<td>0.001</td>
</tr>
<tr>
<td>Prolactin (µg/dl)</td>
<td>10.9 ± 4.9 (3.2–31.7)</td>
<td>9.2 ± 4.9 (1.92–19.6)</td>
<td>0.06</td>
</tr>
<tr>
<td>Insulin fasting (µIU/l)</td>
<td>21.4 ± 19.6 (3.4–132)</td>
<td>13.0 ± 14.3 (1.2–63.7)</td>
<td>0.005</td>
</tr>
<tr>
<td>HOMA (&lt;2)</td>
<td>4.4 ± 4.2 (0.71–27.4)</td>
<td>2.3 ± 2.7 (0.23–13.2)</td>
<td>0.001</td>
</tr>
</tbody>
</table>

Table 3 Comparison of clinical, biochemical, and hormonal parameters of polycystic ovary syndrome (PCOS) and non-PCOS subsets of chronic lymphocytic thyroiditis (CLT) girls with controls.

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>PCOS n = 82</th>
<th>Non-PCOS n = 93</th>
<th>Controls n = 46</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>15.7 ± 2.8 (10.2–25.5)</td>
<td>14.72 ± 1.57 (11–18)</td>
<td>15.9 ± 3.0 (11.9–22.8)</td>
</tr>
<tr>
<td>Ferriman–Gallwey score</td>
<td>13.42 ± 2.5 (8–21)</td>
<td>10.21 ± 3.53 (4–24)</td>
<td>0.03 ± 2.4 (0–7)</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>29.89 ± 4.04 (21–39)</td>
<td>27.03 ± 4.92 (16–39)</td>
<td>25.8 ± 3.7 (17.2–33.3)</td>
</tr>
<tr>
<td>Waist circumference (cm)</td>
<td>74.21 ± 12.29 (52–98)</td>
<td>68.13 ± 12.22 (42–90)</td>
<td>75.1 ± 7.9 (60–88)</td>
</tr>
<tr>
<td>Free T₄ (nmol/dl)</td>
<td>15.17 ± 2.57 (10–22)</td>
<td>16.20 ± 3.0 (11–25)</td>
<td>15.9 ± 3.0 (11.9–22.8)</td>
</tr>
<tr>
<td>BGF (&lt;100 mg/dl)</td>
<td>85.38 ± 12.67 (64–112)</td>
<td>77.69 ± 13.99 (53–127)</td>
<td>69.1 ± 5.9 (56–84)</td>
</tr>
<tr>
<td>Cholesterol (150–200 mg/dl)</td>
<td>209.26 ± 27.17 (142–277)</td>
<td>190.87 ± 26.06 (141–283)</td>
<td>148.8 ± 24.8 (89–198)</td>
</tr>
<tr>
<td>Triglycerides (70–150 mg/dl)</td>
<td>138.94 ± 28.56 (78–198)</td>
<td>128.71 ± 26.70 (86–190)</td>
<td>108.23 ± 20.18 (80–171)</td>
</tr>
<tr>
<td>HDL (&lt;50 mg/dl)</td>
<td>39.07 ± 4.74 (30–51)</td>
<td>38.58 ± 4.67 (26–48)</td>
<td>41.58 ± 6.46 (30–53)</td>
</tr>
<tr>
<td>LDL (70–100 mg/dl)</td>
<td>120.04 ± 17.16 (74–162)</td>
<td>104.47 ± 14.51 (82–164)</td>
<td>99.15 ± 12.12 (80–191)</td>
</tr>
<tr>
<td>Testosterone (0.12–0.7 ng/ml)</td>
<td>0.84 ± 0.52 (0.22–1.93)</td>
<td>0.69 ± 0.38 (0.23–1.80)</td>
<td>0.5 ± 0.2 (0.21–0.82)</td>
</tr>
<tr>
<td>DHEAS (1.2–3.6 ng/ml)</td>
<td>4.70 ± 0.62 (0.54–4.88)</td>
<td>3.66 ± 0.48 (0.38–2.92)</td>
<td>1.6 ± 0.5 (0.4–3.55)</td>
</tr>
<tr>
<td>Cortisol (µg/dl) (morning)</td>
<td>13.97 ± 3.62 (5.78–21.97)</td>
<td>14.74 ± 4.28 (4.17–27.73)</td>
<td>8.1 ± 5.6 (0.51–18.5)</td>
</tr>
<tr>
<td>Insulin fasting (µIU/l)</td>
<td>24.21 ± 23.20 (3.50–113.9)</td>
<td>20.29 ± 19.23 (4.3–132.4)</td>
<td>13.0 ± 14.3 (1.2–63.7)</td>
</tr>
<tr>
<td>HOMA (&lt;2)</td>
<td>5.28 ± 5.54 (0.71–27.4)</td>
<td>3.84 ± 3.36 (0.91–22.3)</td>
<td>2.3 ± 2.7 (0.23–13.2)</td>
</tr>
</tbody>
</table>

*Comparison between PCOS versus non-PCOS. **Comparison between PCOS versus controls. ***Comparison between non-PCOS versus controls. Significance (t-test for independence). a,b,cP≤0.05, d,e,fP≥0.05.

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Discussion

PCOS and IR are reported to be on the rise in the Asian subcontinent, even though systematic studies on this issue are awaited. We have previously reported high prevalence of juvenile autoimmune thyroiditis in young and adolescent girls from India (23). Based on our preliminary observation of high prevalence of PCOS phenotype in these CLT girls during nationwide thyroid surveys and reported high prevalence of thyroid autoimmunity in subjects with established PCOS earlier (11), we undertook this first prospective study to evaluate the association of PCOS with thyroid autoimmunity.

Significantly higher prevalence of PCOS phenotype in CLT girls as compared to controls was noted in the present study for the first time to the best of our knowledge by both Rotterdam 2003 and Sultan & Paris criteria (46.85 vs 4.2%, P<0.001). This observation lends indirect support to the findings of Janssen et al. (11) who conversely reported elevated thyroperoxidase or thyroglobulin antibodies in 26.9% of PCOS subjects in contrast to 8.3% in controls. Besides, they also observed that 42.3% of PCOS subjects had hypoechoic tissue pattern typical of autoimmune thyroiditis on USG in comparison to 6.5% in controls (P<0.001). Familial aggregation and genetic predisposition of these two apparently diverse disorders along with a recent study demonstrating high prevalence of serologic parameters of autoimmunity (anti-histone and anti-dsDNA antibodies) in women with PCOS may suggest the role of autoimmunity in the pathogenesis of PCOS (13–17, 24). Similar findings supporting a potential link between PCOS and autoimmunity have been reported by two other groups (25, 26).

The association of IR and hyperinsulinemia of PCOS with elevation of various cytokines such as IL-4, IL-6, TNF-α, and their alteration after treatment with insulin sensitizers is well established (9, 10). Elevated fasting insulin and HOMA-IR, indicative of significantly higher IR in both of our PCOS and non-PCOS sub-groups of CLT girls when compared to controls, may indicate some pathogenic link between autoimmunity and IR (12, 13). Similarly, higher levels of fasting blood glucose, serum cholesterol and testosterone in non-PCOS subgroup of CLT girls as compared to controls also suggest some commonality in the etiopathogenesis of CLT and PCOS. The non-PCOS subgroup of CLT may be a mild pathophysiologic equivalent of PCOS, and may eventually evolve into fully-fledged PCOS.

Obesity is known to be responsible for IR and associated hyperinsulinemia in women with PCOS, and obese PCOS women have more severe hyperandrogenism and related clinical features (such as hirsutism, menstrual abnormalities, and anovulation) than normal-weight PCOS women (27). Even after BMI adjustment, oligomenorrhea, hirsutism score, serum testosterone, serum insulin, and HOMA values remained significantly high in the cases compared to controls, suggesting that the PCOS pathophysiology in these cases is not due to obesity alone. However, obesity may account for some exaggeration of their clinical phenotype.

Previous data on the interaction of sex steroids and immune regulation have shown that androgens and progesterone can have inhibitory effects and estrogens, a facilitatory effect on humoral immunity. There is evidence that activating immune/inflammatory response is exerted through nuclear factor (NF)κB pathway (28). Though normal to high estrogen coupled with low progesterone milieu in PCOS girls may be considered conducive for the development of autoimmunity, it is difficult to explain the role of hyperandrogenemia. The apparent paradox of positive correlation between anti-TPO antibodies and serum total testosterone observed in our study suggests that the mild hyperandrogenemia typical of PCOS may not be dominant enough to ameliorate autoimmunity. Whether this peculiar hormonal milieu of PCOS is responsible for autoimmunity of CLT (11) or vice versa needs to be pursued in future research.

Hypothyroidism is known to induce a phenotype similar to PCOS or produce features suggestive of metabolic syndrome. The interesting observation of inverse correlation of serum FT4 quartiles with various components of PCOS phenotype in euthyroid CLT girls also lends indirect support to association between PCOS and CLT.

We conclude that the CLT girls have high prevalence of clinical and metabolic derangements suggestive of PCOS as compared to normal age-matched girls. Whether autoimmune thyroiditis predisposes subjects to develop PCOS characteristics or if PCOS is a forerunner of autoimmune thyroiditis, remains an unanswered speculation and mandates follow-up longitudinal studies.

Declaration of interest

The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of the research reported.
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